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ORIGINAL ARTICLE

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Dioxin effects on neonatal and infant thyroid function: routes of perinatal exposure, mechanisms of action and evidence from epidemiology studies

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Abstract *Objectives*: Animal experiments suggest that thyroid function alterations in newborns and infants may represent one of the most sensitive markers of toxicity from 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). Dioxin can be transferred from the mother to the offspring either in utero or through lactation. It has been suggested that thyroid-hormone alterations produced by dioxin in utero or shortly after birth may underlie long-term effects, such as cognitive-ability and neurodevelopment impairment. In the present review article, we appraise available evidence on the effects of perinatal exposure to dioxin on fetal and infant thyroid function. *Methods*: We summarized the routes of perinatal dioxin exposure and research results on possible mechanisms of dioxin toxic effects on thyroid function. We performed a systematic review of epidemiology studies conducted on mother–child pairs exposed to background environmental levels to investigate dioxin effects on neonatal and infant thyroid function. *Results*: Toxicological and mechanistic data indicate that dioxin may impair thyroid function in exposed newborns and infants. Investigations on background-exposed children have not consistently demonstrated an association between perinatal TCDD exposure and thyroid function, although some of the studies suggest that sub-clinical hypothyroidism may be induced by perinatal dioxin exposure within 3 months from birth. Between studies inconsistencies may be related to lab method differences, mixed exposures, and small sample size of the populations evaluated. *Conclusion*: Epidemiology studies have as yet failed to demonstrate an association between perinatal TCDD exposure and thyroid function alterations in human subjects, although suggestive evidence from animal and in-vitro experimental data is available.

Keywords Dioxins · Thyroid gland · Infant · Child · Environmental exposure

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Introduction

Polychlorinated dibenzo-*p*-dioxins (PCDDs) are a group of 75 structurally related compounds, including 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic congener. Dioxins have become widespread environmental contaminants and a potential concern for public health. TCDD shows high persistence in the environment and extremely long half-life in humans (seven or more years) (Michalek et al. 2002). TCDD is detectable at background levels in plasma or adipose tissue of individuals with no specific exposure to identifiable sources, usually at concentrations lower than 10 ppt (parts per trillion, lipid adjusted) (Michalek and Tripathi 1999; Papke et al. 1996). Mean TCDD levels in subjects representative of European and US populations range 2–5 ppt (Aylward and Hays 2002; Papke et al. 1996; Zook and Rappe 1994). Nonetheless, the EPA estimated that in the US population a number of people may have levels up to three-times higher than the average (Aylward and Hays 2002; Flesch-Janys et al. 1996; US EPA 2002), and some population subgroups, exposed to localized sources of contamination, may exhibit concentrations even 20-times higher (Aylward and Hays 2002; Dewailly et al. 1994).

Dioxin effects on humans have been observed after high exposures in historical industrial settings, military operations, or accidental release (Baccarelli et al. 2002, 2005; Bertazzi et al. 2001; Crump et al. 2003; Greene et al. 2003; IARC 1997; Kogevinas 2001; Longnecker

and Daniels 2001; Michalek et al. 2001; Mocarelli et al. 2000; Pesatori et al. 2003; Pohl et al. 2002; Silbergeld 1996; Steenland et al. 2004; US EPA 2002). There has been extensive debate on whether dioxin levels present in the general population, which are 2–3 orders of magnitude lower, are able to elicit the same effects (Kogevinas 2000; Van den Berg et al. 1998). Animal experiments suggest that dioxin may interfere with fetal and infant thyroid function (Birnbaum and Tuomisto 2000; Capen 1994; Kakeyama and Tohyama 2003; ten Tusscher and Koppe 2004). Dioxin can be transferred from the mother to the offspring either in utero or through lactation. Dioxin levels too low to cause toxic effects on the mother may determine alterations and diseases on the fetus and the newborn. Thyroid-hormone alterations produced by dioxin in utero or shortly after birth may underlie long-term effects, such as cognitive-ability and neurodevelopment impairment, given that thyroid hormones are required for brain development in a time-window that begins in utero and spans throughout the first years after birth (Porterfield 2000; Vreugdenhil et al. 2002). Neurotoxic effects of dioxin observed in human studies and animal experiments resemble those seen in fetal and neonatal hypothyroidism (Larsen and Davies 2002). In addition, TCDD-induced alterations of thyroid-hormone levels may be related to increased risk of thyroid cancer, as observed in experimental animals (Capen 2001).

In the present paper, we discuss the potential dioxin effects on neonatal and infant thyroid function. We examine mother-to-child dioxin transfer at current environmental levels of dioxin and its contribution to the child's dioxin body burden. Results from studies uncovering possible mechanisms of dioxin action on thyroid function are described. Finally, we discuss evidence from epidemiology investigations evaluating TCDD-related alterations of thyroid function in newborns and infants.

Routes of perinatal exposure to dioxin

Newborns and infants may represent a subgroup of the population at special risk, because in a sensitive developmental window they may accumulate a dose of dioxin that, as a result of in-utero exposure or breastfeeding, may reach amounts that are higher than those found in the adult population. TCDD internal dose tends to be higher in adult women relative to men, and conditions specific of in-utero exchanges and breastfeeding may cause toxicologically relevant doses of dioxin to build up in newborns and infants.

Gender differences in dioxin accumulation

Dioxin compounds have high affinity for lipids and tend to accumulate in fat tissues (Aylward and Hays 2002). Female subjects have higher proportions of body fat per unit of weight (Aylward and Hays 2002; Koopman-Esseboom et al. 1994; Landi et al. 1998). Therefore, mothers exposed to background dioxin levels may accumulate relatively higher amounts of dioxin that is then transferred to the fetus and breast-fed newborn.

Population studies have shown that dioxin levels, measured in plasma or tissues, are higher in female subjects (Papke et al. 1996; Schuhmacher et al. 1999). This appears to be irrespective of the magnitude of exposure to dioxin sources. For instance, plasma TCDD levels measured approximately 20 years after the Seveso accident exhibited large differences across the contamination zones, but levels measured in female subjects were consistently higher than in men (Landi et al. 1997, 1998). Michalek et al. (2002) observed that mean TCDD half-life in Seveso was 9.6 years among women and 6.5 years among men.

In-utero transfer of dioxin

Detectable concentrations of dioxins have been found in fetal and placenta tissue, cord blood, and amniotic fluid samples (Feeley and Brouwer 2000; Schecter et al. 1990, 1994). While placental dioxin levels reflect both maternal and fetal exposure, cord blood samples are representative of the fetal circulation and reflect in-utero exposure to contaminants. Although there is minimal direct exchange between maternal and fetal blood, the majority of lipid-soluble contaminants seem to be capable of crossing the placental membrane into the fetal circulation by simple diffusion. Fetal exposure to contaminants may also occur through amniotic fluid, which is primarily derived from maternal interstitial fluid. Amniotic fluid is swallowed by the fetus, and absorbed through the respiratory and digestive tracts (Foster et al. 2000).

In stillborns, Kreuzer et al. (1997) found TCDD levels between 1.3 and 2.1 ppt in adipose tissue and 0.76–1.51 ppt in liver tissue. From measurements in maternal blood, cord blood and meconium of three mother–child pairs, Abraham et al. (1996) estimated that prenatal dioxin transfer is approximately equal to 100%. In fact, if dioxin concentrations are expressed on a lipid basis (ppt, lipid adjusted; equivalent to pg/g fat), cord-blood levels are comparable with concentrations in maternal plasma (Feeley and Brouwer 2000; Needham et al. 1991). Similar ranges of dioxin levels are observed in fat extracted from placenta tissue, maternal serum, cord serum, and breast milk (Wang et al. 2004).

Exposure through breastfeeding

Breastfeeding causes the accumulation of a basal dose of dioxin contributing to the total individual body burden: it has been estimated that breastfeeding for 6 months may account for 12–14% of dietary exposure to dioxin until 25 years of age (Patandin et al. 1999). However, such proportion, derived from models based on food

consumption and contamination data, appears to be at variance with the toxicokinetic model developed by Kreuzer et al. (1997) which predicts that the TCDD body burden in breast-fed children declines within a few years to the same background levels reached in children of the same age who had not been nursed.

For lipophilic contaminants, mobilization of maternal fat stores for breast milk production may result in substantial body-burden transfer into breast milk, with subsequent ingestion by breast-fed children; it has been estimated that, on average, the maternal body burden of dioxins decreases by 20–30% during the lactation period (Beck et al. 1994). In industrialized countries, current average concentrations in breast milk of dioxin compounds may range 10–30 ng/kg lipid TCDD toxic equivalent (TEQ) (Abraham et al. 1996; Feeley and Brouwer 2000). On lipid basis, milk dioxin concentrations are similar to those found in the mother's plasma, but, because human milk is rich in lipids, concentrations per unit of total weight are higher in milk than in plasma, and breast-fed babies can attain blood levels greater than those of their mothers (Neubert 1988). An average infant ingests approximately 50–100 pg TCDD TEQ/kg bw/day, 95% of which is absorbed through the digestive tract (Abraham et al. 1996; Feeley and Brouwer 2000). Consequently, levels of nearly all dioxin congeners are from 10 to 15 times higher in nursed than in formula-fed infants (Abraham et al. 1994, 1996).

Mechanisms of dioxin toxic effects on thyroid function

Endocrine functions result from a series of coordinated activities that mediate, together with the nervous and immune systems, appropriate responses to external and internal stimuli (Baccarelli et al. 2000). A variety of chemicals have been identified that may interfere with synthesis, secretion, transport, metabolism, or receptorial actions of endogenous hormones. Analysis of TCDD chemical structure reveals that TCDD bears a structural resemblance to the natural thyroid hormones (Baccarelli et al. 2000; McKinney 1989). Proteins that bind thyroid hormones in vivo may also bind to TCDD and other structure-related compounds. In addition, it has been shown that dioxin increases thyroid-hormone clearance by inducing metabolic enzymes (Capen 1994; Yamada-Okabe et al. 2004).

Regulation of the thyroid axis

The thyroid gland produces two related hormones, thyroxine (T_4) and triiodothyronine (T_3), which play a critical role in cell differentiation during development and help maintain thermogenic and metabolic homeostasis in the adult (Fig. 1) (Jameson 2004). Thyroid hormone production is regulated by the thyroid stimulating hormone (TSH), secreted by the thyrotrope cells of the anterior pituitary which are controlled by the hypothalamus through the thyrotropin-releasing hormone (TRH). Circulating T_4 and T_3 are bound to binding proteins. Only the unbound hormone, which represents a very small portion of total serum concentrations, is biologically available to the tissues. Therefore, measurement of free T_4 (FT_4) and free T_3 (FT_3) reflects biologically active thyroid hormones, while total T_4 (TT_4) and total T_3 (TT_3) measure both bound and unbound fractions. Thyroid-axis function is based on a feedback control, a process that tends to maintain free T_4 and T_3 concentration within a narrow range. A small reduction of thyroid hormones triggers a rapid increase of TRH and TSH secretion, resulting in thyroid gland stimulation and increased thyroid hormone production. Because its variations are much larger than those of T_4 and T_3 and its levels can be accurately measured in serum, TSH is considered the most sensitive marker of thyroid hormone action. TSH increases in sub-clinical

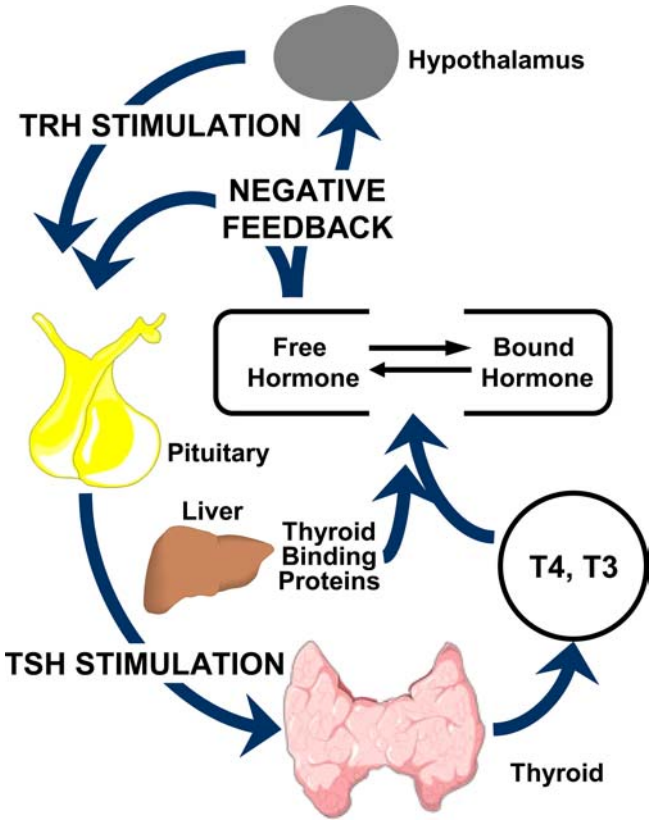

Fig. 1 Thyroid function control and interrelationships between thyrotropin-releasing hormone (*TRH*), thyroid-stimulating hormone (*TSH*), thyroxine (*T_4*), triiodothyronine (*T_3*), and thyroid binding proteins. Thyroid hormones T_4 and T_3 feedback to inhibit hypothalamic production of TRH and pituitary production of TSH. Animal studies, considered together with thyroid-axis regulation mechanisms, suggest that TCDD exposure may cause the following hormonal patterns: (1) sub-clinical hypothyroidism (isolated increase in serum TSH levels and normal free serum T_4 and T_3; due to decreased negative feedback consequent to lower tissue availability/action of T_4 and T_3); (2) overt hypothyroidism (increased serum TSH levels and decreased free serum T_4 and T_3). Levels of total serum T_4 and T_3 (bound + unbound) may vary depending on serum concentrations of thyroid binding proteins

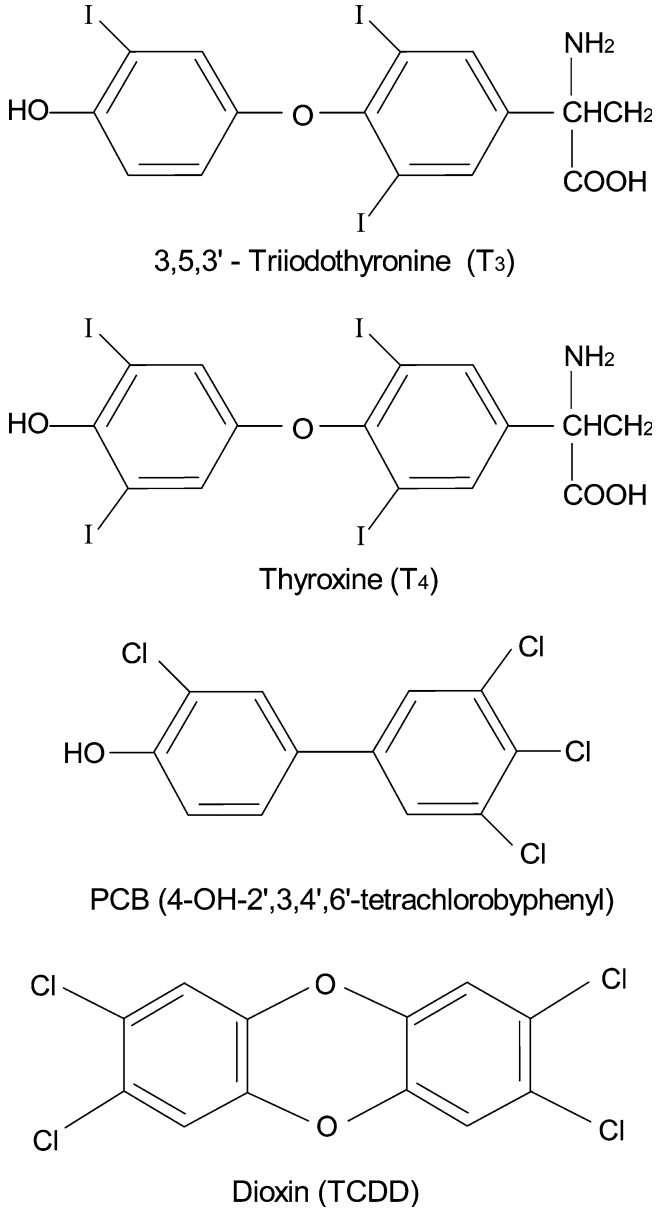

Fig. 2 Common structural properties of thyroid hormones, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCCD), and coplanar polychlorinated biphenyls (*PCBs*)

and clinically apparent primary hypothyroidism and decreases when thyroid hormones are produced in excess (Jameson 2004).

Structure similarities between TCDD and thyroid hormones

Molecular modeling studies revealed that dioxins and thyroid hormones share common molecular reactivity properties and possibly similar molecular recognition in biochemical systems (McKinney et al. 1985). These molecular properties include a somewhat rigid, sterically accessible aromatic ring with hydrophobic lateral substituents (Fig. 2). Qualitative structure requirements for high toxicity include planarity or coplanarity of structure in a shape approximating a rectangle and a sufficient degree of halogenation concentrated in lateral positions (McKinney 1989).

The observation of structure similarities between TCDD and thyroid hormones prompted structure-activity relationship (Cheek et al. 1999; McKinney and Waller 1998) and in-vitro competitive binding studies (Cheek et al. 1999; McKinney 1989) that confirmed that TCDD properties resemble those of thyroid hormones triiodothyroxine (T_3) and thyroxine (T_4) (Porterfield 2000). However, affinity of dioxin-like compounds is low for thyroid receptor and elevated for serum transport proteins (Cheek et al. 1999). Recent data showed that dioxins may inhibit post-receptorial events induced by thyroid hormones (Birnbaum and Tuomisto 2000; Bogazzi et al. 2003), suggesting an antagonist receptorial activity of the tested compounds.

Interference with binding proteins

Dioxin competition may displace thyroid hormones from binding proteins, thus increasing their elimination rates. This would contribute to the hypothyroidism-like hormonal alterations described in dioxin toxicity studies, characterized by low T_4 and low T_3 circulating levels and elevated TSH concentrations. Animal studies have indicated that such competition mechanism exists for transthyretin, a serum protein that binds most of circulating T_4 and a small proportion of T_3 (Birnbaum and Tuomisto 2000; Capen 1994).

In humans, only 11% of circulating T_4 and 9% of circulating T_3 are bound to transthyretin, while the glycoprotein thyroid-hormone binding globulin (TBG) binds about 68% of T_4 and 80% of T_3 (Lingappa and Mellon 1997). Although TCDD also exhibits binding activity toward human TBG (Brouwer and van den Berg 1986; McKinney 1989), between-species differences in transport-protein binding may account for the seemingly greater sensitivity of the rat thyroid, relative to humans, to develop hyperplastic and/or neoplastic nodules in response to chronic TCDD-induced TSH stimulation (Capen 2001).

Induction of thyroid-hormone metabolizing enzymes

In animals, thyroid-hormone concentrations are decreased by enhanced liver glucuronidation, which is the rate-limiting step in biliary excretion of T_4 and T_3 (Sewall et al. 1995). Thyroxine is metabolized by UDP-glucuronosyltransferase (UGT) to a glucuronide, and then excreted in the bile (Birnbaum and Tuomisto 2000; Porterfield 2000; Ritter 2000; Sewall et al. 1995; Van Birgelen et al. 1995; Yamada-Okabe et al. 2004). The induction of conjugating enzymes, such as UGT, as well as of a number of drug-metabolizing enzymes, is a

well-known biochemical effect of TCDD, which is mediated via the AhR pathway (Baccarelli et al. 2004; Landi et al. 2003; Safe 1995; Schrenk 1998; Sewall et al. 1995). Genetic variations, within the AhR pathway, have been identified that may determine individual responsiveness to dioxin (Landi et al. 2005).

In rats, long-term TCDD exposure induces glucuronidation and appears to contribute to TCDD-related changes of circulating thyroid hormones. Increased glucuronidation has been associated with chronic stimulation of the thyroid secondary to the activation of compensatory TSH-mediated hypothalamic-pituitary-thyroid feedbacks (Capen 2001; Okino and Whitlock 2000) and with the risk of developing tumors derived from thyroid follicular cells (Capen 1994; Okino and Whitlock 2000; Sewall et al. 1995).

Systematic review of epidemiology evidence

Methods for study selection and data extraction

To document any published association between TCDD and thyroid function alterations, we performed a PubMed (National Library of Medicine, Bethesda, MD, USA) systematic search of all studies published from 1966 through December 2004. We used the search query [“thyroid,” “triiodothyronine,” “thyroxine,” “thyroid hormones,” “thyrotropin,” “T_3,” “T_4,” OR “TSH”] AND [“TCDD,” “tetrachlorodibenzodioxin,” OR “dioxins”]. We performed a recursive hand search of cited bibliographies to increase completeness. Two investigators (S.M.G. and A.B.) independently reviewed all titles and on-line abstracts retrieved by the literature search. The following inclusion criteria had to be fulfilled: (1) Inclusion of human subjects. (2) Exposure to TCDD. Studies on subjects exposed to organochlorine compounds that did not include TCDD were not considered. (3) Measurements of T_3 (free or total), T_4 (free or total) and/or TSH available in the study. (4) English language. Disagreements were resolved by consensus with reference to a third reviewer (P.A.B.), if necessary. Articles fulfilling inclusion criteria were divided in two groups according to the route and age at exposure: (a) Perinatal studies, including newborn or children who were exposed to dioxin in utero or through breastfeeding (Table 1). (b) Studies on adult subjects (Table 2). Six articles on perinatal dioxin exposure and seven on adult subjects could be identified. Data were extracted (S.M.G) on to an electronic database based on a previously piloted data extraction form. Extracted data were type and number of participants, exposure sources, exposure characteristics, thyroid function parameters, and observed outcomes.

Literature search results

Epidemiology investigations conducted on children (Table 1) have primarily evaluated the association of serum hormone levels in infants between 0 and 3 years of age with the concentrations of dioxin compounds measured in breast milk of their mothers. Mother–child pairs were not exposed to specific sources of dioxin and their TCDD levels were relatively low, similar to those found in the general population.

Pluim et al. (1992, 1993) observed higher mean concentrations of TSH, total T_4, and T_4/TBG ratio at 11 weeks after birth among children who had been exposed to milk total TEQ levels of dioxin and dioxin-like compounds higher than the median of the population evaluated. Total T_4 and T_4/TBG ratio were higher also in the first week. Iodine excretion in urine at all time intervals was not correlated with TEQ levels. The observed hormonal pattern was suggestive of TCDD-related resistance to thyroid-hormone action at the tissue level (Larsen and Davies 2002). The authors hypothesized that exposure to dioxin-like compounds interfered with transport of T_4 into the cell, and its subsequent conversion into T_3, or with T_3 binding to its nuclear receptor. In a subsequent examination conducted at 2–2.5 years of age, no association between thyroid hormone levels and the original exposure scale was observed (Ilsen et al. 1996).

In the Netherlands, Koopmann-Esseboom et al. (1994) reported changes in thyroid hormone concentrations in pregnant mothers and their infants exposed to background levels of PCDDs, polychlorinated dibenzofurans (PCDFs), and polychlorinated biphenyls (PCBs). Total T_4, total T_3, free T_4, and TSH were measured in serum samples from the mothers in the last month of pregnancy and after delivery, in plasma from the umbilical cord, and in serum from infants at the second week and the third month after birth. The study included 78 children, breastfed for at least 6 weeks. Higher TEQ levels in milk were significantly correlated with lower maternal total T_3 and total T_4 levels. In the children, exposure to milk total TEQs above the median level was associated with higher infant plasma TSH at the second week and third month after birth. Although transient alterations of total T_4 were observed, infant free T_4 was not altered, resembling the hormonal pattern found in patients with sub-clinical hypothyroidism (Larsen and Davies 2002).

In a study conducted in Japan, PCDD, PCDF and coplanar-PCB concentrations were measured in milk collected about 3 months after delivery (Nagayama et al. 1998). Breast milk TEQ levels were used to calculate an index of total TEQ-intake by taking into account individual breastfeeding duration and average intake of breast milk. Significant negative correlations were observed between estimated total TEQ intakes and serum levels of T_3 and T_4 measured at 1 year of age. No indication was reported on whether assays for free or total T_3 and T_4 were used. No changes in TSH were observed.

In a second Japan study, PCDDs, PCDFs and PCBs were measured in breast milk collected 30 days after birth. Blood was taken at the age of 1 year from infants

Table 1 Results from epidemiology studies on children investigating the effects of TCDD and other PCDDs on thyroid function

References	Size	Exposure	Range of total TEQ levels in breast milk (ng TEQ/kg)		Main findings in the high exposure group	Dose–response relationship
			Low exposure group	High exposure group		
Pluim et al. (1992, 1993), Ilsen et al. (1996)	$n = 34$	PCDDs, PCDFs, PCBs	8.7–28.0	29.2–62.7	Higher TSH and total T_4 at 11 week. No association at 2–2.5 years of age	Not assessed
Koopman-Esseboom et al. (1994)	$n = 78$	PCDDs, PCDFs, PCBs	12.4–30.8	30.8–76.4	Higher TSH at second week and third month, with no change in free T_4, and total T_3. Decrease in total T_4 at second week	Present, shape not defined
Nagayama et al. (1998)	$n = 36$	PCDDs, PCDFs, PCBs	15.2–48.5[a]		Lower total T_4 and T_3 at 1 year of age; no change in TSH	Linear
Matsuura et al. (2001)	$n = 337$	PCDDs, PCDFs, PCBs	5–55[b]		No change in serum TSH, total T_3, total and free T_4 at 1 year of age	Not present
Nagayama et al. (2004)	$n = 100$	Dioxins, unspecified	< mean TEQ intake[c]	> mean TEQ intake[c]	No change in thyroid hormones at 1 years of age	Not assessed

PCBs polychlorinated biphenyls, *PCDDs* polychlorinated dibenzo-*p*-dioxins, *PCDFs* polychlorinated dibenzofurans, *TEQ* toxic equivalent, *TSH* thyroid-stimulating hormone, T_3 triiodothyronine, T_4 thyroxine

[a]Subjects were not divided in low and high exposure groups. Linear correlation between estimated total TEQ intake and thyroid function parameters was tested through correlation analysis

[b]Total approximated range derived from Fig. 3 of the Matsuura et al.'s paper. Subjects were not divided in low and high exposure groups. Linear correlation between milk TEQ levels and thyroid function parameters was tested through correlation analysis

[c]Estimated mean TEQ intake of the entire study group was not reported in the paper. Median TEQ intake was equal to 29 ng-TEQ/kg body weight

who had been breastfed (Matsuura et al. 2001). Total serum T_3 and T_4, free T_4 and TSH levels were within normal ranges and not correlated with TEQ concentrations in breast milk. In addition, no differences of thyroid-hormone levels were found when the breast-fed infants were compared with a control group including bottle-fed children.

Nagayama et al. (2004) examined in male and female children the effects of lactational exposure to organochlorine pesticides, PCBs and dioxins on serum levels of T_3, T_4, TSH and TBG. No association of breast-milk dioxin TEQs with thyroid hormones measured in children of 1 year of age was found. The association of different toxicants with thyroid-hormone levels was separately analyzed.

No studies were conducted on newborns or children exposed to dioxin levels higher than those normally found in background-exposed populations. Most of the existing cohorts with high dioxin exposure are based on industrial workers or military personnel and almost exclusively include male adult subjects (IARC 1997; Kogevinas 2001; Steenland et al. 2004). However, studies on adult thyroid function have been conducted in a number of those highly exposed populations (Table 2). The largest study, conducted on 1,009 Vietnam Air Force Veterans and 1,429 unexposed subjects, showed, in agreement with animal data, elevated TSH levels in individuals with higher TCDD body burden (Pavuk et al. 2003). The other investigations were based on a much smaller number of subjects and produced inconsistent results (Table 2) (Calvert et al. 1999; Johnson et al. 2001; Nagayama et al. 2001; Ott et al. 1994; Pavuk et al. 2003; Zober et al. 1994).

In summary, results of epidemiology studies conducted on newborns and infants are sparse. Investigations that measured thyroid-hormone levels at 1 year of age or later found no changes in TSH. Conversely, the two studies that evaluated thyroid function within 3 months from birth showed elevated circulating TSH in subjects with higher exposure, with no consistent decrease of T_3 and T_4. High serum TSH has been indicated as the most reliable marker of hypothyroidism in newborns and children (Delange 1999). Between-studies discrepancies in T_3 and T_4 levels may reflect complex time-specific actions of dioxin compounds, but also methodological differences. The critical issues we

Table 2 Results from epidemiology studies on adult subjects investigating the effects of TCDD and other PCDDs on thyroid function

References	Population	Exposure	Main findings
Jennings et al. (1988)	2,4,5-TPA production workers ($n = 18$) and unexposed referents ($n = 15$)	TCDD	None of the subjects had biochemical evidence of thyroid dysfunction
Ott et al. (1994)	BASF autoclave accident ($n = 131$ exposed subjects, $n = 141$ unexposed referents)	TCDD	Positive associations of serum TCDD with TBG and total T_4
Zober et al. (1994)	Exposed ($n = 158$), unexposed ($n = 161$) chemical workers	TCDD	Clinical thyroid disease more frequent in the exposure group
Calvert et al. (1999)	2,4,5-TCP production workers ($n = 281$) and unexposed referents ($n = 260$)	TCDD	Higher mean free thyroxin index among highly exposed workers
Johnson et al. (2001)	2,4,5-TPA sprayers ($n = 37$)	TCDD	Serum TCDD levels inversely associated with T_3 and TSH
Nagayama et al. (2001)	Yusho accident exposed subjects ($n = 16$)	PCBs, PCDDs, PCDFs	No association with T_3, T_4, TSH
Pavuk et al. (2003)	Vietnam Air Force Veterans ($n = 1{,}009$ exposed, $n = 1{,}429$ unexposed subjects)	TCDD	Positive correlation between TSH and serum TCDD levels

PCBs polychlorinated biphenyl, *PCDDs* polychlorinated dibenzo-*p*-dioxins, *PCDFs* polychlorinated dibenzofurans, *TCDD* 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, *TCP* trichlorophenol, *TEQ* toxic equivalent, *TPA* trichlorophenoxyacetic acid, *TSH* thyroid-stimulating hormone, *T_3* triiodothyronine, *T_4* thyroxine

identified in conducting our literature review were lab method differences, small sample size of the populations, and mixed exposures. The investigations showed differences in the assays used to assess thyroid hormones. Some of the studies assayed for total T_4 and T_3 concentrations, which include both free and protein-bound circulating hormones, while others have measured free T_4 and T_3, which reflects the levels of biologically active hormones available to the tissues. Total hormone concentrations may be altered by several known determinants (estrogen levels, illness, medications, genetic factors) of serum binding protein levels (Larsen and Davies 2002), which may act as confounders in epidemiology investigations. It is worth noting that most studies based on measurement of total thyroid hormones have not formally taken into account such possible confounders. Often, populations evaluated were small and possibly inadequate to assess subtle effects that may be associated with background dioxin levels. In addition, most studies classified the exposure using the cumulative TEQ levels, resulting from the sum of several different dioxin and dioxin-like compounds. Effects specific to TCDD or other individual congeners may have been missed using such an analytical strategy.

Conclusions

Toxicological and mechanistic data indicate that dioxin may impair thyroid function in exposed newborns and infants. The results of our systematic literature search indicate that studies on background-exposed children have as yet failed to consistently demonstrate an association between perinatal TCDD exposure and thyroid function. However, some of the available evidence suggests that sub-clinical hypothyroidism may be induced by dioxin exposure within 3 months from birth. Between studies inconsistencies may be related to sample size limitations and methodological issues, including mixed PCB and dioxin congener exposure that has precluded conclusions about dioxin congeners per se. Further understanding of toxicological mechanisms, including the relationship between AhR pathway activation and thyroid function, will be critical to the definition of dioxin individual responsiveness and perinatal toxicity.

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